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NATURETIN AND NAQUA

Chlorothiazide (Diuril - Merck), hydrochlorothiazide (various manufacturers), flumethiazide (Ademol - Squibb) and hydroflumethiazide (Saluron - Bristol) (see The Medical Letter, 1:9, 1959; 2:6, 1960) are eminently useful drugs with clinically similar diuretic and metabolic properties and similar side effects. Two new thiazide derivatives, benzydroflumethiazide (Naturetin - Squibb) and trichlormethiazide (Naqua - Schering), differ from the parent compounds by virtue of side-chain substitutions which slow their rate of removal from the circulation, and thus prolong their action. It has yet to be shown, however, that the difference in duration of effect is clinically significant.

EVALUATION OF THIAZIDES - The following considerations should be kept in mind in evaluating claims made for the various thiazide agents:

(1) Patients resistant in diuresis to one derivative are likely to be resistant to the others.

(2) For any patient, each of the drugs has a "ceiling dose" above which a further increase in dose yields no appreciable increase in urinary sodium loss. Doses much lower than the ceiling doses are usually adequate. The recommended average doses per 24-hour period are: for chlorothiazide and flumethiazide, 500 mg.; for hydrochlorothiazide and hydroflumethiazide, 50 mg.; for benzydroflumethiazide, 5 mg.; and for trichlormethiazide, 4 mg. These doses produce roughly similar losses of sodium and water when given to normal subjects or to patients with edema. It should of course be understood that with any thiazide, different patients will require different doses, and that the same patient will vary in his dosage requirements. Furthermore, the average daily dose recommendation neglects the effect of dosage schedules. The effect of a 4-times-daily dosage of chlorothiazide clearly exceeds that of the same total dose given once daily. For the longer-acting thiazides - Naturetin and Naqua - a twice-daily schedule is probably more effective than the same total dose given once daily.

(3) Despite the evidence that effective doses of chlorothiazide produce greater loss of potassium and bicarbonate in normal animals or man than do comparable doses of the newer analogs, in edematous patients clinically significant differences in potassium loss with the various thiazide derivatives have not been demonstrated. Losses of potassium with any thiazide are likely to be influenced

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less by the structure of the derivative than by the duration and total dosage of thiazide therapy and the nature of the disease being treated. For example, in some patients with severe congestive heart failure or cirrhosis of the liver, and in patients depleted of sodium by dietary or diuretic measures (such as the thiazides themselves), there is often excessive secretion of aldosterone, causing accelerated loss of potassium and greatly curtailed loss of sodium. Patients are sometimes advised to liberalize salt intake with these diuretics in order to suppress the potassium loss due to hyperaldosteronism, but since the major usefulness of the drugs is to rid the body of sodium, it would seem better to impose modest restriction of sodium intake and to use smaller doses of drug together with potassium supplements. Potassium supplements should, in fact, be used with the newest analogs just as with the older ones (The Medical Letter, 2:6, Jan. 22, 1960).

SIDE AND ALLERGIC EFFECTS - With newer derivatives as well as with chlorothiazide, blood uric acid may rise and attacks of gout may be precipitated; diabetes may become aggravated or manifest for the first time; and liver decompensation may be precipitated. Photosensitization has been reported with hydrochlorothiazide as well as with chlorothiazide, and similar effects may appear with the newer thiazides. Hypersensitivity reactions, including skin rashes, allergic purpura and severe glomerulonephritis (E. W. Fitzgerald, Jr., AMA Arch. Int. Med., 105:305, 1960) have also been noted. It cannot be assumed that drug sensitivity reactions will be diminished by the reduced milligram dosage. All of the thiazide drugs should be used with due respect for potentially serious reactions.

With many patients, once-a-day dosage may be adequate with the newer derivatives. Except for this advantage of convenience, there appears to be no reason to recommend any one of the thiazides, including Naturetin and Naqua, as superior to the other drugs in this group. The cost of all of the drugs is about the same (about $11 per hundred 500-mg. tablets of Diuril or the equivalent).

MIRADON, A NEW ANTICOAGULANT

A new oral anticoagulant, anisindione (Miradon - Schering), is claimed to have advantages over the other available prothrombinopenic agents because of "low toxicity, uniformity and predictability of response, speed of action, and absence of cumulation." It is a member of the indandione family and chemically related to phenindione (Hedulin - Walker; Danilone - Schieffelin) and diphenadione (Dipaxin - Upjohn).

COMPARISON WITH OTHER DRUGS - Five favorable clinical studies of the preparation have appeared in the English medical literature, but none of them were controlled by the concomitant use of other drugs. When studied under controlled conditions by a Medical Letter consultant, Miradon was found to be as good as but no better than bishydroxycoumarin USP (Dicumarol), acenocoumarin (Sintrom - Geigy) and Dipaxin, the drugs with which it was compared.

The peak prothrombinopenic effect occurs about 36 hours after oral administration. This is not significantly more rapid than the effect of other commonly used agents. The manufacturer recommends an induction program for adults of

300 mg. the first day, 200 mg. the second, and 100 mg. the third. Although the average maintenance dose is about 100 mg. daily, the range is wide (25 to 250 mg.) and the effect of any given amount appears to be no more predictable, uniform, or "smooth" than that obtained with other anticoagulants.

LIKE PHENINDIONE - The evidence available at the present time suggests that Miradon has very nearly the same characteristics as phenindione and that they are approximately equal in effect on a milligram-for-milligram basis. The excretion products of both, particularly during the induction period, may impart a red color to the urine if it is alkaline. Although no cases of agranulocytosis due to Miradon administration have been reported, its chemical similarity to phenindione suggests the possibility of this complication.

The editors of The Medical Letter believe that the physician should continue to use the anticoagulant with which he is familiar and proficient. If he has been unable to maintain stable anticoagulant control in a patient with other agents, he will probably do no better with Miradon. If he has reason to change to one of the indandiones, however, Miradon appears to be on a par with others in this group (see "Oral Anticoagulant Drugs," The Medical Letter, 1:85, Nov. 13, 1959). With this drug, as with others, concurrent heparin injections will in most cases be advisable in the induction period; the patient should always have available 5 or 10 mg. tablets of phytonadione USP (vitamin K_1) (Mephyton - Merck; Konakion - Roche) to control bleeding; and frequent determination of prothrombin time is essential.

A 100-mg. maintenance dose of Miradon costs the patient about 15¢ per day, as compared with 12¢ for 100 mg. of Hedulin and 5¢ for 100 mg. of Dicumarol.

ANTIHISTAMINES FOR ALLERGIC DISORDERS

The more antihistamines are studied, the clearer it becomes that there is no "best" antihistamine preparation. All of the antihistamines offered for the relief of allergic symptoms are generally effective in appropriate dosage, but their side effects vary from patient to patient, and the choice among them for any one patient often involves a trial-and-error search for a preparation relatively free of unwanted effects.

SEDATIVE EFFECTS - Sedation, the most important of antihistamine side effects, can be dangerous to a patient who must drive a car or operate a machine; but sedation is often a welcome effect where the irritability associated with the allergic process interferes with sleep and increases the severity of all symptoms. Probably no antihistamine is completely free of sedative effects. Those which most frequently have marked sedative effects are Phenergan, Benadryl and Decapryn. In some persons, particularly children, antihistamine drugs may act as stimulants. Other side effects include muscular weakness, dryness of the mouth, nose and throat, and gastrointestinal disturbance.

DURATION OF EFFECT - The differences in duration of action among antihistamine preparations can often be used to advantage. With most antihistamines

a single dose provides protection for only about four hours, but some (see below) are likely to be effective for considerably longer periods. Liquid preparations of the longer-acting drugs may be useful for small children who cannot take "sustained-action" tablets or capsules.

USEFULNESS - Antihistamines are usually not effective in bronchial asthma. Drugs that are effective, particularly epinephrine and similar adrenergic agents, are best employed to reverse bronchoconstriction and vasodilatation. Though they seldom give more than partial relief, the antihistamine drugs have their greatest usefulness in the symptomatic treatment of allergic rhinitis, particularly seasonal hay fever, and urticaria. They have some effect on anaphylactic symptoms, but epinephrine is more effective and acts faster; therefore it should be used first in a severe reaction.

Antihistamines are well absorbed when given by mouth and effects are usually apparent within a half hour. For more rapid effect, parenteral forms of Dimetane, Chlor-Trimeton and Benadryl are available. Topical preparations of many antihistamines are still marketed despite their ineffectiveness and the risk of contact sensitization to the drug. The sustained-action forms of various antihistamines are widely used, and many persons find them entirely satisfactory. In some persons, however, absorption may be excessively rapid or too slow. Furthermore, the speed of absorption may vary from day to day in the same person.

DOSAGE AND COST - The following table shows the usual adult dosages of various antihistamines and approximate cost (when prescribed in quantities of 100):

For sedative effect:		
Diphenhydramine USP (Benadryl - Parke, Davis)	50 mg.	4.5¢
Doxylamine USP (Decapryn - Merrell)	25 mg.	5.5¢
Tripelennamine USP (Pyribenzamine - Ciba)	50 mg.	5.5¢
Promethazine (Phenergan - Wyeth)	25 mg.	11¢
For prolonged effect:		
Triprolidine (Actidil - B-W)	2.5 mg.	5¢
Chlorcyclizine USP (DiParalene - Abbott; Perazil - B-W)	50 mg.	4.5¢
Pyrrobutamine (Pyronil - Lilly)	15 mg.	3.5¢
Promethazine (see above)		
Other widely used antihistamines include:		
Bromodiphenhydramine USP (Ambodryl - Parke, Davis)	25 mg.	4.5¢
Chlorpheniramine USP (Chlor-Trimeton - Schering)	4 mg.	5¢
Carbinoxamine (Clistin - McNeil)	4 mg.	5¢
Diphenylpyraline (Diafen - Schenlab; Hispril - SKF)	2 mg.	5¢
Parabromdylamine (Dimetane - Robins)	4 mg.	5¢
Dexbrompheniramine (Disomer - White)	2 mg.	5¢
Methapyriline USP (Histadyl - Lilly; Thenylene - Abbott)	50 mg.	4.5¢
Dextrochlorpheniramine (Polaramine - Schering)	2 mg.	5¢
Pyrilamine USP (Neo-Antergan - Merck; and other brands)	50 mg.	2-5¢
Phenindamine USP (Thephorin - Roche)	25 mg.	4¢
Isothipendyl (Theruhistin - Ayerst)	4 mg.	4¢

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